

Scientific Abstract

Cancer vaccine clinical trials performed over the last few years have demonstrated that patients can be immunized against specific tumor antigens. Studies performed by our group, targeting the HER-2/neu (HER2) antigen, have demonstrated that HER2 specific T-cell precursor frequencies can be significantly boosted and epitope spreading can be elicited with active immunization. Epitope spreading indicates that a cancer patient is developing a native immune response to multiple epitopes from a specific antigen (intramolecular spreading) as well as multiple antigens (intermolecular spreading) present in existing tumor. Thus, both the magnitude as well as the character of the immune response elicited with immunization may be important in predicting vaccine efficacy. Cancer, however, is not caused by a single genetic alteration but rather by multiple genetic alterations and the function of multiple aberrant proteins. A problem facing tumor immunologists today is how to vaccinate cancer patients against multiple antigens involved in the malignant transformation. Plasmid DNA based immunization offers a technology that is easily adapted to the delivery of multiple antigens driving the malignant process. Immunization with plasmid DNA, however, has not resulted in the reproducible generation of systemic immunity in a variety of models of infectious disease antigens. The disappointing clinical translation of DNA vaccines may be due, in part, to the inefficient transfection of non-professional antigen presenting cells (APC) in tissues such as muscle, via intramuscular injections, and thus poor trafficking of APC to draining lymph nodes for initiation of a systemic immune response. We hypothesize it will be possible to improve the efficacy of in vivo APC transfection with DNA vaccines by the use of local soluble cytokines such as GM-CSF. GM-CSF has great utility and safety as a vaccine adjuvant. Local influx of skin Langerhans' cells (LC) induced by GM-CSF and application of plasmid DNA to the dermis rather than muscle may improve the efficacy of DNA vaccines. Studies have demonstrated that the intracellular domain (ICD) of HER2 is immunogenic in cancer patients. When this domain of HER2 is formulated as a plasmid DNA vaccine and used to vaccinate against breast cancer in a murine model, HER2 ICD specific immunity could protect animals from tumor development. Such data suggests that the HER2 ICD is not merely an immunogenic protein in patients with breast cancer, but has the potential to be a "tumor rejection" antigen.

The aims of this clinical trial are to (1) determine the safety of a HER2 ICD plasmid based DNA vaccination in patients with advanced stage HER2 overexpressing breast and ovarian cancer, (2) determine the immunogenicity of a HER2 ICD plasmid based DNA vaccination, (3) determine if the dose of a HER2 ICD plasmid based DNA vaccine effects the development of an immune response, and, (4) determine whether intra and intermolecular epitope spreading occurs with HER2 ICD DNA immunization. The long-term goal will be to use this study as a platform to develop multi-antigen plasmid based vaccines for the prevention of common solid tumors.